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EXAMINER
STANDLEY, STEVEN H

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,228	TSIEN, JOE Z.	
	Examiner	Art Unit	
	Steven H. Standley	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/9/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *1-27 and 35-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/04&10/05*. 4/07
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Unity of Invention

It is noted that applicant has elected Group IV containing claims 29-34 in the paper dated 3/09/05, with (partial) traverse. Applicant argues that Groups II and V should be rejoined because Group II, which is a transgenic animal, would be useful in the method of Group V, which is an in vivo method of screening compounds (remarks, 3/09/05, 3rd paragraph). Applicant also states that it would not be an undue burden. However, this is *not* found to be persuasive for two reasons: 1) groups II and V are both directed to non-elected subject matter, and 2) the groups lack unity of invention for reasons made of record in the action dated 1/10/05. In particular, Groups II and V require different non-coextensive considerations. Group II requires the consideration of each animal type and how NMDA receptors are related to their learning and memory, whereas Group V requires a consideration of what direct and indirect methods may be used to assay changes in each animal. Therefore rejoinder of the above groups would be a substantial and undue search burden on the examiner.

Applicant also requests the rejoinder of Groups III, IV and VIII. However, the groups lack unity of invention for the reasons made of record in the requirement for restriction dated 1/10/05. In particular Group III requires a consideration of the structure of reporter genes and what promoter elements are required, Group IV requires a consideration of what nucleic acids are may be used in what cells, and Group VIII requires a consideration as to how to stimulate NMDA receptors. Since the

considerations are non-coextensive, rejoinder of the above groups would be a substantial and undue search burden on the examiner. It is noted that since applicant has amended claim 28 in the response of 3/09/05, the examiner has rejoined claim 28 in part to the elected invention of group IV, claim 28 will be considered as it reads upon a method of identifying compounds that enhance learning and memory by affecting NR2B expression or NMDA activity comprising providing a pair of cells, one of which expresses an exogenous nuclei acid encoding NR2B.

Claims 28-34 are under consideration.

Claim Objections

Claims 29-34 are objected to because of the following informalities: Claims 29-34 are dependent on claim 28, which is directed a non-elected invention. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a method of identifying compounds that enhance NR2B expression in a subject by, a) isolating a hipocampal pyramidal cell from a transgenic mouse that overexpresses NR2B, b) administering a candidate compound to

a non-transgenic isolated hippocampal pyramidal cell from a mouse, c) comparing *synaptic NMDA* receptor peak current or *synaptic NMDA* receptor current decay time of the treated, non-transgenic hippocampal pyramidal cell, to the untreated isolated hippocampal pyramidal cell from the transgenic mouse overexpressing NR2B, and d) wherein an increase in synaptic NMDA receptor peak current or decay time of the treated non-transgenic hippocampal cell such that it is equivalent to the synaptic NMDA receptor peak current and decay time in the untreated transgenic cell, is indicative that the test compound increases expression of NR2B, does not reasonably provide enablement for a method for identifying compounds that enhance learning and memory in a subject by increasing expression of [or activity of nmda receptors] nr2b in a subject which comprises exposing a cell in vitro to a test compound suspected of upregulating nr2b wherein the determining step comprises comparing NMDA receptor function of a treated, non-transgenic cell with NMDA receptor function of said transgenic cell comprising an exogenous nucleic acid molecule encoding nr2b, wherein a change in the NMDA receptor function in the treated, non-transgenic cell that comprises the same features of the NMDA receptor function exhibited in the transgenic cell being indicative that the test compound enhances learning and memory in a subject by affecting nr2b expression or NMDA receptor activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This is not enabling for the given the scope of the claims because nearly all of the 'features' of NMDA receptor function in the transgenic mouse disclosed in the

specification are not unique to, nor are they necessarily mediated by, an increase in NMDA receptor expression. Therefore measurement of such 'features' would not reasonably result in selecting for compounds that increase NMDA receptor expression or function. Secondly, both prior and post-filing date disclosures by the instant applicant and others indicate the invention does not work in a manner disclosed by the specification or in a manner commensurate with the scope of the claims. It should be noted also that if the invention is shown not to be enabled in post-filing disclosures, the invention could not been enabled at the time of filing.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

With respect to the instant application, the state of the art, the nature of the invention, the level of predictability in the art, the breadth of the claims, the amount of guidance given by the inventor, and the quantity of experimentation needed to make or use the invention are the most pertinent factors in determining that the experimentation needed in order to make and use the invention as disclosed would be undue.

The nature of the invention is a method of identifying compounds that enhance learning and memory by increasing the expression of the NMDA receptor subunit, NR2B, or by enhancing the activity of NMDA receptors. The method relies on the comparison of the effect of a compound on a normal cell to a transgenic cell that overexpresses the NR2B subunit of the NMDA receptor. A transgenic mouse, and a cell from that transgenic mouse are disclosed in the specification, and exhibit electrophysiological and behavioral 'features' that indicate enhanced learning, and memory. The logic is that, by comparison, if a test compound causes the same 'features' in a normal cell or mouse as that exhibited by the cell of, or the transgenic mouse itself, then that indicates the test compound enhances learning and memory by affecting expression of NR2B or activity of NMDA receptors.

The prior art indicates that one can enhance NMDA receptor activity (function) by administration of a compound and have ***no effect*** on learning and memory, and perhaps even negatively effect learning and memory. Figure 2 and 3 (described on page 9-10 of the specification) discloses several electrophysiological features of normal mice to those overexpressing NR2B. In particular, transgenic mice feature enhanced NMDA receptor current mediated by NR2B (as evidence by Figure 2D-F and Figure 3B). Figure 7A-C (described on page 12 of the specification) also discloses the feature that the mice overexpressing NR2B perform significantly better in acquisition and retention of the Morris Water Maze, a behavioral test of learning and memory. In contrast, the prior art has shown that *administration of a compound (BDNF) to a non-transgenic pyramidal cell* of a hippocampal neuron causes a significant increase in

NMDA receptor activity, specifically from NR2B-containing receptors (see Figure 1-3A, pages 259-261; Crozier et al, 1999; Learning and Memory), and yet Intracerebroventricular administration of that compound to an animal (BDNF) does not enhance learning retention as measured by the same Morris Water Maze as Figure 7 of the specification (Cirulli et al, 2000, Neuroscience letters; see Figure 1, page 208, especially 'time in zone,' notice that BDNF injection trends toward inhibiting retention as measured by less time spent in the quadrant formerly containing the submerged platform). In this case, an increase in NMDA receptor function has nothing to do with learning and memory. This indicates that the *art is highly unpredictable* for identifying a compound as claimed in claims 29-34.

The specification gives *guidance* as to measuring expression levels of NMDA receptors (see figure 1C), and to measuring *synaptic* peak NMDA receptor current (Figure 2D of specification), *synaptic* NMDA receptor decay time (Figure 2F, which reasonably distinguishes the increased presence of the NR2B subunit). However, *the specification gives no guidance and there are no working examples directed at the relationship between NMDA receptor* ***activity*** (as apposed to increased expression) and electrophysiological or cognitive measures. Moreover, as mentioned above, the prior art indicates NMDA receptor activity is not related to enhanced learning and memory. Therefore one skilled in the art would not know how to make and use the invention for identifying compounds that enhance learning and memory by modulating NMDA receptor activity.

The prior art indicates there are many other ways, not dependent on NMDA receptor function, to enhance learning and memory. Therefore all but the most specific measures, uniquely attributable to NR2B receptor overexpression, would not select for compounds that enhance learning and memory by specifically affecting NR2B. For instance, administration of nicotine, which is a nicotinic cholinergic receptor agonist, enhances acquisition and retention in the Morris Water Maze (Socci et al, 1995; see Figure 1 on page 858, which is an acquisition curve, and Table I which is the summary of the retention test), and in fear conditioning (Gould et al, 2004, Behavioral Brain Research; see page 170, figure 1B), which are behavioral tests in which mice overexpressing NR2B 'featured' enhanced performance, and which are encompassed by the broad claim 29, and specifically recited as behavioral tests in claim 33. Furthermore, enhanced performance in tasks of learning and memory is not unique to administration of nicotine. For instance, administration to an animal of a phosphorylated growth factor receptor fragment that affects the phosphoinositide-3-kinase pathway (which reasonably has nothing to do with NMDA receptors) enhances learning memory as measured by the fear conditioning and Morris Water Maze tests used in the instant application (see abstract, Figure 3E for fear conditioning, and Figure 4 for Morris Water Maze; Dash et al., 2004). The instant specification also teaches a behavioral test of novel object recognition (Figure 4A and B of the specification), and shows that mice overexpressing NR2B feature enhanced exploratory preference of a novel object. This feature is also not unique to compounds that affect NMDA receptors. Hampson et al (1998, Journal of Neuroscience) report that an 'ampakine,' which increases only AMPA

receptor activity, also enhances performance in a task called 'delayed non-matching to sample' which requires the animal to select a novel object over an object displayed earlier (explained on page 2741 2nd paragraph) to receive a reward. Figure 3 (page 2743) of Hampson et al shows that administration of an ampakine (CX516) significantly increases performance compared to control in the task.

The specification discloses that enhanced long-term-potentiation (LTP; figure 3C-D) is an electrophysiological feature of the transgenic mice overexpressing NR2B, which is ecompassed by claims 29-32. The art indicates that enhanced LTP in a mouse can also be associated with impaired performance in learning and memory tasks. Therefore, enhanced LTP is not a unique feature of either NMDA receptor overexpression, nor is it a feature necessarily associated with enhanced learning and memory. For instance, Uetani et al. (2000; EMBO Journal) show that mice deficient for Protein Tyrosine Phosphatase (PTP) have ***impaired acquisition and retention*** in the Morris Water Maze (Figure 4, page 2778), and significantly ***enhanced*** LTP (Uetani, page 2780 Figure 6G-H, described in lines 9-13 of the figure legend). This indicates enhanced LTP is not a unique feature of mice overexpressing NR2B. Further, enhanced LTP can be produced by compounds that affect proteins other than NMDA receptors. For instance, Chien et al (2003; Molecular Pharmacology) disclose a compound called YC-1 which dramatically enhances LTP (page 1323, figure 1 top of legend and graph Figure 1A) that activates guanylyl cyclase, which generates the intracellular second messenger cGMP (cyclic guanine monophosphate) and acts by

affecting the extracellular signal-regulated kinase (ERK) and phospho-cAMP response element binding protein (CREB; see abstract, Chien et al., 2003).

Further, The specification discloses that enhanced long-term-potentiation (LTP; figure 3c-d) is an electrophysiological feature of the transgenic mice overexpressing NR2B, and the art indicates that NR2B-containing NMDA receptors ***do not mediate LTP,*** but only mediate long-term depression (LTD). Liu et al (2004; Science) disclose, using compounds very specifically blocking NR2B-containing receptors, that blocking NR2B-containing receptors only blocks LTD and not LTP. Figure 1A (page 1021) shows that induction of LTD is inhibited with both ifenprodil and Ro25-6981, and Figure 1C shows that these compounds don't affect LTP (explained on page 1021, in column 3). In fact, another NMDA receptor subunit, NR2A, mediates LTP (see figure 3 on page 1022, explained in columns 2-3) as demonstrated by the use of compound NVP-AAM077. While LTP is one non-unique feature of mice overexpressing NR2B, Liu et al. indicates that it cannot be a feature of a *non*-transgenic cell expressing NR2B or a *non*-transgenic cell having enhanced (nr2b containing) NMDA receptor activity. In other words, in order to exhibit the features of the transgenic cell overexpressing NR2B, applicant must demonstrate the clearly unique feature that the compound administered to the non-transgenic cell causes NR2B subunits of the non-transgenic cell to become directly involved with the mediation of LTP, and not LTD as set forth by Liu et al.

The breadth of the invention as currently claimed is such that one skilled in the art could not make or use the invention measuring "the same features of NMDA receptor function exhibited in the transgenic cell [currently part of clam 29]" because

none of the features related to behavioral tests and nearly all the features related to electrophysiological measures are not unique to, and do not specifically measure the features of NMDA receptor function exhibited in the transgenic (as it relates to claims 29-32, and 34). Also, The specification gives *guidance* as to measuring *synaptic* peak NMDA receptor current, *synaptic* NMDA receptor decay time (which reasonably distinguishes the increased presence of the NR2B subunit), however claim 33, which is related to these measurements, does not recite measurement of *synaptic* peak *NMDA* receptor current (only), or *synaptic NMDA* channel decay time (only), and therefore are not claims to measurements that are unique to the transgenic.

In claim 29, applicant claims "a transgenic cell" and "a non-transgenic cell." However, post-filing date work by the inventor in the instant application along with others directly indicates that the invention does not work in cells of the visual cortex (Philpot et al., 2001; Neuropharmacology) of the transgenic mouse disclosed in the instant specification. Philpot et al disclose that the transgenic mice overexpressing the NR2B subunit do not exhibit differences in LTP in visual cortex (page 766; figure 1), and do not exhibit differences in synaptic NMDA receptor decay time (page 767; figure 2B). Furthermore, transgenic mice overexpressing NR2B do not exhibit enhanced learning in an olfactory-dependent learning task (see abstract; White and Youngentob, 2004; Brain Research). Therefore, the art indicates applicants' invention does not work in "a transgenic cell," because it does not work in cortical cells of the transgenic mice overexpressing NR2B and it does not work in olfactory bulb cells of the transgenic mice overexpressing NR2B. Furthermore, the specification only teaches the use of a

hippocampal transgenic pyramidal cell, and given the obvious unpredictability of the invention one skilled in the art could not expect to use the invention other than in a pyramidal cell of the hippocampus from the transgenic mouse overexpressing NR2B.

Given the nature of the invention, the state of the art which discloses that applicants invention will not work as claimed, the high level of unpredictability in the art, the lack of guidance in the specification, and the scope of the claims, one skilled in the art could not make or use the invention as disclosed in the specification, nor as claimed, without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-34 are rejected under 35 U.S.C. 112, 2nd paragraph as being indefinite.

The term "comprises the same features" in claim 29 is a relative term which renders the claim indefinite. The term "comprises the same features" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. One of ordinary skill in the art would not know what constituted "comprising the same features" because the meets and bounds of a 'feature' of NMDA receptor function in the transgenic comparison are unclear. Claims 30-34 are rejected as they depend on an indefinite claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication should be directed toward examiner Steven Standley (Ph: 571-272-3432). The examiner can normally be reached Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the Steven Standley fail, the examiners' supervisor, Anthony Caputa, can be reached at (571 272-0829).

Information regarding the status of an application may be obtained from the Patent Application Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (toll free) 866-217-9197.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

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Steven H. Standley, Ph.D.
4/28/05

Bridget E. Bunner
patent examiner